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USAARL REPORT NO. 71-23

EFFECT OF ISONIAZID ON PERFORMANCE II

By

Mark A. Hofmann, CPT, MS

Richard O. Nossaman, SP/5, U.S. Army

JUNE 1971

U. S. ARMY AEROMEDICAL RESEARCH LABORATORY

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ABSTRACT

Seventeen aviators who converted from negative to positive on a tuberculosis tine test performed a variety of laboratory tests given before, during and after INH therapy. INH was administered prophylactically at dosage levels of 300 mg. per day for one year. The tasks consisted of reaction time (auditory and visual), rotary pursuit tracking, mental multiplication and digit span. The data did not indicate that the drug adversely affected performance, on any of the tasks utilized.

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Commanding

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EFFECT OF ISONIAZID ON PERFORMANCE II

INTRODUCTION

This study represents one part of a tripartite study carried out in conjunction with Lyster Army Hospital and the Neurology Branch of the U. S. Army Aeromedical Research Laboratory. The study was initiated upon request of the Aviation School when a number of civilian instructor pilots became tuberculin converters. They were subsequently placed on isoniazid (INH), a prophylactic drug for tuberculosis. Typically, it has been the policy of the US Army to recommend this treatment for one year if tuberculin skin tests convert from negative to positive. During this period, converters on flying status serving the US Army are normally grounded. This action was called into question at Fort Rucker for two reasons: 1) the manpower loss, and 2) the lack of evidence of debilitating effect of INH on performance.

The Aviation Psychology Division was asked to determine if this chemotherapy at dosage levels of 300 mg. per day had an effect on performance. A review of the literature indicated isoniazid at some dosage levels was said to produce side effects of: peripheral neuropathy; constipation; diarrhea; peresthesia; hyperflexia; muscular twitch; delay in micturition; convulsions; psychoses; fatigue; impairment of concentration memory and depression[1,2,3,4,5,6,7,8].

With respect to performance, a study by Olsen and Torning[9] demonstrated differences between scores on a "subtle test" for patients receiving INH therapy. These differences occurred between scores taken before treatment began and scores taken two months into the treatment period. No differences were found between pre-treatment and post-treatment scores. They contended this test demonstrated a tendency for INH patients to forget things in the peripheral part of the attention sphere. Thus, they concluded, "Although the reported

psychological side effects do not contraindicate the use of isoniazid in tuberculous patients, we feel they speak in favor of a certain caution in using isoniazid prophylactically on a large scale in healthy people." Isoniazid in this study was administered at dosage levels of 4 mg. per kilogram of body weight combined with para-aminosalicylate (PAS) at 200 mg. per kilogram of body weight. PAS was discounted as producing the above effects based on previous observations by the authors, of patients treated with streptomycin (SM) and PAS.

A study by Simon[10] indicates that isoniazid therapy does not have an adverse psychological effect. Simon administered the Rorschach, Minnesota Multiphasic Personality Inventory (MMPI), Scale of Inner Maladjustment (SIM), Bell Adjustment Inventory, An Inventory of Factors STDCR, The Guilford-Martin Inventory of Factors (GAMIN), Wechsler Memory Scale and Digit Symbol, to patients before INH therapy and again six months after treatment was initiated. None of these psychological tests revealed any negative effects. However, some positive effects were noted. The author concluded, "Most essential is that the results of the study bear out the general hypothesis that patients under Isoniazid therapy do not show deleterious psychological effects."

Theodore and Wolff[11], in a very well controlled study, did not find any drug effect when comparing school ratings between approximately 800 children taking isoniazid and 800 taking a placebo. Nor, did they find that school performance was related to amount of medication prescribed. They concluded if isoniazid has any effect on the mental ability of children, it was too slight to be detected by their study.

Simmons and Ambler[12], reported that they observed no significant adverse drug effects which would constitute a flight safety hazard for a group of Naval aviator tuberculin converters taking 300 mg. of isoniazid daily. Their subjects were evaluated on a variety of physiological and performance measures.

The object of the present study was to measure the performance of a group of instructor pilots taking isoniazid. Performance measures were taken on a number of laboratory tasks to determine if they would be affected by this chemotherapy. This report will contain information from a previous report by Nossaman and Hofmann[13] combined with data collected on an additional eight subjects.

METHOD

Subjects

Subjects were seventeen rotary-wing aviator instructors between the ages of 41 and 57. This group had a mean age of 48.

Performance Tasks

Rotary Pursuit Tracking (RPT). The rotary pursuit tracking device utilized a twelve inch disc with a round target, one inch in diameter placed one inch from the edge. The twelve inch disc was rotated at 26 rpm and Time on Target (TOT) was measured in seconds to the nearest tenth of a second on a Cramer Timer. All tracking trials lasted two minutes. Tracking took place with no ancillary tasks and also while performing mental multiplication and digit span.

Mental Multiplication (MV). This task consisted of presenting a series of five multiplication problems from a slide projector. Problems were projected directly in front of the subject. The exposure time for each problem was held constant at four seconds. After this four second period, the problem was removed and the subject gave his answer. Time to respond was measured by a Standard Electric Timer. This timer measured in 1/100 of a second. Measurements were also taken as to the accuracy of response. This task was performed during a two minute tracking trial.

Digit Span Visual (DV). This task required the subject to repeat from memory visually presented digits, while tracking. The presentation mode was the same as that utilized with the visual multiplication problems. The span of digits was seven in length and a series of five were given to each subject. Measurements were taken with regard to response time and accuracy of response.

Mental Multiplication Auditory (MA). In this task, the subject received five mental multiplication problems aurally. Each problem took 1.5 seconds to present after which the subject gave his answer. Time to respond was recorded as well as errors in response. Problems were delivered over head-phones which had 46 db SPL of pink noise at all times except when problems were given. This task was done simultaneously while tracking.

Digit Span Auditory (DA). This task was administered in the same manner as the MA task described above with the exception that, instead of multiplication, a series of seven digit spans were delivered.

Each digit span took seven seconds to present and all were presented during a two minute tracking trial.

Visual Reaction Time (VRT). This task consisted of responding to a red light which was energized randomly at inter-signal intervals of three, four, and five seconds. When the light came on, a clock started which ran until the subject responded by pushing a hand-held micro-switch. This response terminated the light and the clock and also indicated the start time of the next inter-signal interval. Reaction time was measured to the nearest 1/100 of a second by a Standard Electric Timer. The subjects did not track while performing this task.

Auditory Reaction Time (ART). This task was administered in the same manner as the visual task described above except that in this case the stimulus was a 46 db SPL pink noise signal delivered through the head-phones.

Procedure

Subjects were tested several days before beginning chemotherapy. This pre-trial constituted the control trial. Subjects were seated in an experimental room and given a standardized set of instructions. The first task was visual reaction time followed by auditory reaction time. The VRT task consisted of 13 trials. Three practice trials followed by ten test trials. The ART was administered in the same manner. After these tests were completed, standardized instructions were given for the tracking tasks. Before the testing session began, a two minute practice trial was given. Following this, a two minute tracking trial with no ancillary tasks was initiated. This was followed by a one minute rest period after which tracking tasks with mental multiplication and digit span were given. Preceding each trial were practice trials. Between the multiplication and digit span tasks which were presented both visually and aurally, one minute rest periods were given. All tracking tasks were two minutes in length. The total test time per person was approximately 35 minutes. After Trial I, the same procedure was repeated on: Day 43 after therapy started (Trial II); Day 181 of treatment period (Trial III); Day 300 of treatment period (Trial IV); and seven days after cessation of the drug treatment (Trial V).

RESULTS

One way analyses of variance with repeated measures on one factor were chosen over two factor analyses of variance treating subjects as a factor. This was done because a review of the data revealed no systematic trends for individual subjects and for the purpose of this study, trial effects for the group were considered of primary importance. The significance level chosen was .01 or less for all tests. Each score used in the analyses of the auditory and visual digit span and mental multiplication data is a mean of five measures. Scores used in the reaction time analyses are based on the mean of ten measures and the missed responses and tracking scores are based on one measure per subject for each trial. Newman-Keuls a posteriori tests were performed on data found to be significant in the analyses of variance.

Tracking (Time on Target Scores - TOT). TOT scores across the trials for tracking under the conditions of: no ancillary tasks (CT); mental multiplication with problems presented visually (TMV); mental multiplication with problems presented aurally (TMA); digit span with digits presented visually (TDV); and performing digit span with digits presented aurally (TDA), were found to be significant at .01 level, as indicated in Tables 1, 2, 3, 4, and 5.

Table 1.

Summary of Analysis of Variance
Control Tracking - CT

Source	SS	df	MS	f
Between Subjects	2817.68	16		
Within Subjects	6162.13	68		
Trials	3369.35	4	842.34	19.30**
Residual	2792.77	64	43.64	
Total	8979.81	84		

**p < .01

Table 2.

Summary of Analysis of Variance
Tracking - TMV

Source	SS	df	MS	f
Between Subjects	3053.54	16		
Within Subjects	6257.70	68		
Trials	1922.12	4	480.53	7.09**
Residual	4335.58	64	67.74	
Total	9311.24	84		

**p < .01

Table 3.

Summary of Analysis of Variance
Tracking - TMA

Source	SS	df	MS	f
Between Subjects	1428.57	16		
Within Subjects	2798.73	68		
Trials	688.58	4	172.14	5.22**
Residual	2110.15	64	32.97	
Total	4227.30	84		

**p < .01

Table 4.

Summary of Analysis of Variance
Tracking - TDV

Source	SS	df	MS	f
Between Subjects	4579.56	16		
Within Subjects	7008.37	68		
Trials	2719.09	4	679.77	10.14**
Residual	4289.28	64	67.02	
Total	11587.93	84		

**p < .01

Table 5.

Summary of Analysis of Variance
Tracking - TDA

Source	SS	df	MS	f
Between Subjects	1776.38	16		
Within Subjects	3076.62	68		
Trials	764.64	4	191.16	5.29**
Residual	2311.98	64	36.13	
Total	4853.00	84		

**p < .01

Post-hoc tests performed on these significant results can be found in Tables 6, 7, 8, and 9.

Table 6.

Tests on Differences Between Totals
Control Tracking - CT

Ordered Trials		I	II	III	IV	V
	Totals	1647.9	1836.6	1899.9	1931.6	1934.3
I	1647.9	--	188.7**	252.0**	283.7**	286.4**
II	1836.6		--	63.3	95.0	97.7
III	1899.9			--	31.7	34.4
IV	1931.6				--	2.7
V	1934.3					--
Truncated range r			2	3	4	5
$q_{.99}$ (r, 64)			3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)			102.41	116.57	125.29	131.28

**p < .01

Table 7.

Tests on Differences Between Totals
Tracking - TMV

Ordered Trials		I	II	III	V	IV
	Totals	1578.0	1724.6	1754.0	1794.1	1799.7
I	1578.0	--	146.6**	176.0**	216.1**	221.7**
II	1724.6		--	29.4	69.5	75.1
III	1754.0			--	40.1	45.7
V	1794.1				--	5.6
IV	1799.7					--
Truncated range r			2	3	4	5
$q_{.99}$ (r, 64)			3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)			127.60	145.24	156.10	163.57

**p < .01

Table 8.

Tests on Differences Between Totals
Tracking - TMA

Ordered Trials		I	II	III	V	IV
	Totals	1799.9	1866.3	1908.2	1923.0	1931.2
I	1799.9	--	66.4	108.3**	123.1**	131.3**
II	1866.3		--	41.9	56.7	64.9
III	1908.2			--	14.8	23.0
V	1923.0				--	8.2
IV	1931.2					--
Truncated range r			2	3	4	5
$q_{.99}$ (r,64)			3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)			89.02	101.33	108.91	114.11

**p < .01

Table 9.

Tests on Differences Between Totals
Tracking - TDV

Ordered Trials		I	II	III	V	IV
	Totals	1504.6	1640.0	1724.5	1752.3	1761.9
I	1504.6	--	135.4**	219.9**	247.7**	257.3**
II	1640.0		--	84.5	112.3	121.9
III	1724.5			--	27.8	37.4
V	1752.3				--	9.6
IV	1761.9					--
Truncated range r			2	3	4	5
$q_{.99}$ (r,64)			3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)			93.18	106.07	114.00	119.45

**p < .01

Table 10.

Tests on Differences Between Totals
Tracking - TDA

Ordered Trials		I	II	III	V	IV
	Totals	1791.4	1834.6	1898.9	1903.7	1930.1
I	1791.4	--	43.2	107.5	112.3	138.7**
II	1834.6		--	64.3	69.1	95.5
III	1898.9			--	4.8	31.2
V	1903.7				--	26.4
IV	1930.1					--
Truncated range r			2	3	4	5
$q_{.99}$ (r,64)			3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)			93.18	106.07	114.00	119.45

**$p < .01$

For CT, TMV, and TDV Time on Target, it can be seen that Trials II, III, IV and V are significantly different from Trial I, while not differing one from another. The post-hoc tests for TMA-TOT indicate that Trials III, IV and V differed from Trial I and were not different from one another. In addition, they did not differ from Trial II which was not statistically different from Trial I. For TDA-TOT, Trial IV differed from Trial I with no other differences present.

Mental Multiplication: Mental Multiplication presented visually (MV) and aurally (MA) was performed while tracking. MV and MA scores (time to respond) analyses can be found in Tables 11 and 12.

Table 11.

Summary of Analysis of Variance
Multiplication Visual - MV

Source	SS	df	MS	f
Between Subjects	247.86	16		
Within Subjects	167.44	68		
Trials	31.24	4	7.81	3.67**
Residual	136.19	64	2.13	
Total	415.30	84		

**p < .01

Table 12.

Summary of Analysis of Variance
Multiplication Auditory - MA

Source	SS	df	MS	f
Between Subjects	178.30	16		
Within Subjects	120.76	68		
Trials	29.13	4	7.28	5.09**
Residual	91.63	64	1.43	
Total	299.06	84		

**p < .01

MV and MA across trials were significant at the .01 level. The post-hoc test for MV (Table 13) shows Trial II differed from Trial IV with no other differences existing. For MA (Table 14), Trial I differed from II, IV and V while no other differences were indicated.

Table 13.

Tests on Differences Between Totals
Multiplication Visual - MV

Ordered Trials		IV	V	III	I	II
	Totals	63.41	72.52	73.07	84.72	92.86
IV	63.41	--	9.11	9.66	21.31	29.45**
V	72.52		--	.55	12.20	20.34
III	73.07			--	11.65	19.79
I	84.72				--	8.14
II	92.86					--

Truncated range r	2	3	4	5
$q_{.99}(r,64)$	3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}(r,64)$	22.62	25.74	27.67	28.99

**$p < .01$

Table 14.

Tests on Differences Between Totals
Multiplication Auditory - MA

Ordered Trials		V	IV	III	II	I
	Totals	85.98	86.15	86.37	96.65	111.50
V	85.98	--	.17	.39	10.67	25.52**
IV	86.15		--	.22	10.50	25.35**
III	86.37			--	10.28	25.13**
II	96.65				--	14.85
I	111.50					--

Truncated range r	2	3	4	5
$q_{.99}(r,64)$	3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}(r,64)$	18.55	21.12	22.70	23.78

**$p < .01$

Digit Span: Digit Span measures were taken while the subjects tracked, and were in two forms, time to respond and correctness of response. The digits were presented visually (DV) and aurally (DA). Analysis of variance indicated that there were no significant trial effects for the time measures or missed responses.

Reaction Time: The analysis of visual reaction time (VRT) and auditory reaction time (ART) scores across trials were significant as can be seen in Tables 15 and 16.

Table 15.

Summary of Analysis of Variance
Visual Reaction Time - VRT

Source	SS	df	MS	f
Between Subjects	.049	16		
Within Subjects	.113	68		
Trials	.063	4	.016	20.07**
Residual	.050	64	.001	
Total	.162	84		

**p < .01

Table 16.

Summary of Analysis of Variance
Auditory Reaction Time - ART

Source	SS	df	MS	f
Between Subjects	.052	16		
Within Subjects	.050	68		
Trials	.019	4	.005	9.76**
Residual	.031	64	.0005	
Total	.102	84		

**p < .01

Post-hoc tests on the Visual Reaction Time (Table 17) reveal Trials IV and V differed from Trials I, II and III while not differing from one another. The Auditory Reaction Time (Table 18) post-hoc tests yielded results indicating Trials IV and V differed from Trials I and II with no other differences present.

Table 17.

Tests on Differences Between Totals
Visual Reaction Time - VRT

Ordered Trials		I	II	III	IV	V
	Totals	3.89	4.09	4.34	4.96	5.04
I	3.89	--	.20	.45	1.07**	1.15**
II	4.09		--	.25	.87**	.95**
III	4.34			--	.62**	.70**
IV	4.96				--	.08
V	5.04					--
Truncated range r			2	3	4	5
$q_{.99}$ (r,64)			3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)			.49	.56	.60	.63

**p < .01

Table 18.

Tests on Differences Between Totals
Auditory Reaction Time - ART

Ordered Trials		I	II	III	IV	V
	Totals	2.87	2.97	3.17	3.45	3.51
I	2.87	--	.10	.30	.58**	.64**
II	2.97		--	.20	.48**	.54**
III	3.17			--	.28	.34
IV	3.45				--	.06
V	3.51					--

Truncated range r	2	3	4	5
$q_{.99}$ (r, 64)	3.76	4.28	4.60	4.82
$\sqrt{nMSres}\ q_{.99}$ (r,64)	.35	.39	.42	.44

**p < .01

Analyses of false responses indicated that false responses to visual and auditory signals were significant over trials (Tables 19 and 20). Table 21 shows the total missed responses for the trials.

Table 19.

Summary of Analysis of Variance
False Responses - VRT

Source	SS	df	MS	f
Between Subjects	156.85	16		
Within Subjects	195.20	68		
Trials	37.34	4	9.34	3.78**
Residual	157.86	64	2.47	
Total	352.05	84		

**p < .01

Table 20.

Summary of Analysis of Variance
False Responses - ART

Source	SS	df	MS	f
Between Subjects	156.612	16		
Within Subjects	350.400	68		
Trials	72.071	4	18.018	6.479**
Residual	177.988	64	2.781	
Total	507.012	84		

**p < .01

Table 21.

Total False RT Responses
Visual & Auditory

	Trials				
	I	II	III	IV	V
Visual	29	33	32	8	9
Auditory	31	40	40	9	3

DISCUSSION

Inasmuch as many tests were performed, the confidence level for any one test when viewing the study in its entirety was not .99. Thus, one cannot place too much emphasis on any one test showing significance. Another thing that must be remembered is the fact that this was an experiment of opportunity and as such, controls were not always as rigorous as one might desire. For example, each subject was not tested at the same time of day, nor was there a control group. The post-hoc tests on control tracking (no ancillary tasks), tracking while performing visually presented multiplication problems, and tracking while performing digit span presented visually, had the same result. Trial I was in every case significantly different from subsequent trials and in all cases indicated the poorest performance. One explanation of this, can be made in terms of learning, that is to say, learning took place in tracking performance, which would indicate that the practice trials did not bring learning to an asymptote. If this were the case, it can be concluded that if there were a decrement produced by the drug, it was not of sufficient magnitude to offset this learning effect. In addition, since the other trials are not significantly different from one another, there does not seem to be any cumulative drug effect of a deleterious nature nor any withdrawal effects. Another explanation of the results could be made in terms of the drug improving performance. This would be tenuous without further research and would not explain why the performance of Trial V (after cessation of the drug) did not differ from Trials II, II and IV. The above discussion pertains to tracking while performing mental multiplication presented aurally with the only difference being that Trial II did not show a significant difference from Trial I. The task of tracking while performing digit span presented aurally, had a lesser trial effect with only Trial IV being statistically significant from Trial I. If the hypothesis is accepted that learning contributed to trial effects, this is not a wholly unexpected result. For aviators are quite used to receiving and responding to digital auditory information while performing tracking tasks, so learning effects would be expected to be less. In any event, this result indicates no drug effect. In general, if the drug did effect one's ability to attend to tasks as might be suspected from some of the literature[9], this was not found in the case for the tracking tasks used in this study, because Trial I with no drug was never significantly better than subsequent trials with or without drug.

Scores on multiplication of visually and aurally presented problems yielded significant trial effects. In the visual problem task only Trial II was significantly slower than Trial I while latter trials were not significant one from another or Trial I. At present, there is no explanation for this result, however, the authors are not of the opinion that it supports the conclusion that drug effect was present. The post-hoc tests for multiplication of aurally presented problems indicated the later trials of II, IV and V were significantly better than Trial I. This result does not support a detremental drug effect, or at least, one of such a magnitude to offset any learning that may have been present. Therefore, no significant trial effects for digit span be they presented visually or aurally. Therefore, it would appear that isoniazid does not adversely affect these kinds of memory and mental manipulation tasks. In addition, missed responses, on digit span and mental multiplication for both aural and visual presentation produced no significant trial effects. This would indicate that the drug did not impair mental performance in terms of correctness of response over trials.

Visual and auditory reaction times indicated a significant trial effect, with Trials IV and V producing significantly slower reaction times than Trials I, II and III for the former and Trials IV and V being slower than Trials I and II for the latter. This result is perhaps best explained in terms of the false response data for the reaction time measures. This data revealed statistically significant trial effects with earlier trials having larger numbers of false responses than later trials. This would indicate a high anticipatory reaction resulting in faster responses while producing more false responses or responding before the signals appeared. On the other hand, Trials IV and V indicated slower false responses, indicating that on these trials subjects waited for a signal before responding which would lead to longer reaction times but more accuracy. The largest mean reaction time difference between Trials V and I (VRT) was .068 seconds. Though statistically significant, in most cases it is not practically significant and in light of the reduction of false responses, which at a minimum is 20, indicates that performance improved on the latter trials. It is unlikely that the drug produced this result since Trials IV and V are not different, and Trial V occurred after cessation of the drug. A better explanation for such behavior might be offered in terms of familiarity with the task which could have lead to the extinction of trying very hard to be "super-quick."

CONCLUSION

Performance on the tasks utilized in this investigation was not adversely affected by INH taken prophylactically at dosages of 300 mg. daily.

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APPENDIX

Test Problems

Mental Multiplication

Visual	Auditory
13 x 4	75 x 2
68 x 6	77 x 3
52 x 6	64 x 4
48 x 8	45 x 8
87 x 6	98 x 5

Digit Span

Visual	Auditory
3298229	1590400
3174939	7114843
7285274	643841
8689311	3389640
3032297	4403552